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(54) Title: HYPOGLYCEMIC SULFONYL PYRAZOLONES AND PYRAZOLINES

(57) Abstract: This invention provides compounds and their pharmaceutically acceptable salts, pharmaceutical formulations of said compounds, and methods for treating hyperglycemia associated with non-insulin dependent diabetes and for treating hyperlipidemia.

HYPOGLYCEMIC SULFONYL PYRAZOLONES AND PYRAZOLINES**FIELD OF THE INVENTION**

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This invention relates to the treatment and control of hyperglycemia, such as occurs in non-insulin-dependent diabetes mellitus (NIDDM). This invention also relates to treatment and control of hyperlipidemia.

10

BACKGROUND OF THE INVENTION

The disease, diabetes mellitus, is recognized in two forms. Type I diabetes requires exogenous insulin for control of the disease because it appears that endogenous production of insulin by the Isles of Langerhans in the pancreas is extremely poor or non-existent. Type I diabetes is often referred to as insulin-dependent diabetes mellitus (IDDM). Type II, non-insulin-dependent diabetes mellitus (NIDDM), is characterized by defects of insulin sensitivity in peripheral tissues such as adipose tissue and muscle, as described by J. E. Gerich in *New Engl. J. Med.*, 321, 1231-1245 (1989).

25

Hyperlipidemia is often observed in diabetics (*Diabetes Care*, 18, Supplement 1, 86-93, 1995). The combination of hyperlipidemia and hyperglycemia greatly increases the risk of cardiovascular diseases in diabetics. Successful treatment of hyperlipidemia and hyperglycemia in diabetics is needed urgently.

30

Blank reviewed hypoglycemic agents (*Burger's Medicinal Chemistry*, 4th Ed., Part II, John Wiley and

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Sons, N.Y., 1979, 1057-1080). Newer hypoglycemic agents were reviewed by Hulin in *Progress in Medicinal Chemistry*, 31, ed. G. P. Ellis and D. K. Luscombe, Elsevier Publishing Co., 1993.

5

Currently, partial control of NIDDM is achieved by a diet and exercise regimen, by administration of exogenous insulin, by administration of hypoglycemic agents, (e.g. the sulfonylureas), or by some combination of these
10 protocols. Sulfonylureas, such as chlorpropamide, acetohexamide and tolbutamide, are useful orally-effective hypoglycemic agents achieving success in the control of NIDDM in a number of patients. However, drugs currently available for the control of the hyperglycemia
15 associated with type II diabetes mellitus (NIDDM) possess significant liabilities or limitations of efficacy. (Ellingboe, et al., *J. Med. Chem.* 36:2485-2493, 1993). Considerable effort has been expended toward developing novel, orally-administered antihyperglycemic drugs. A
20 preferred therapeutic approach for treating NIDDM incorporates drugs that counteract insulin resistance rather than those that stimulate endogenous insulin secretion. (J. R. Colca and D. R. Morton, *New Antidiabetic Drugs*, ed. C. J. Bailey and P. R. Flatt, Smith-Gordon and Company, Ltd., London, Chapter 24,
25 1990). Drugs that treat insulin resistance are called insulin sensitivity enhancers.

Sato, Y, et al. (*Diabetes Research and Clinical Practice*, 12:53-60, 1991) described the hypoglycemic
30 effect of D-phenylalanine derivatives. In normal dogs, the hypoglycemic activity of the compound was greater than that of tolbutamide but less than that of glibenclamide. The compounds exerted a rapid

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hypoglycemic effect and improved glucose tolerance in genetically diabetic KK mice and in streptozotocin-treated rats. Yamasaki, et al. disclosed a group of 2-quinolone derivatives showing antidiabetic activity in
5 NIDDM (WO 92/21342).

Some known hypoglycemic compounds also reduce serum cholesterol or triglyceride levels. (Clark, et al., U.S. Patent No. 5,036,079). The combination of these
10 biological activities in one compound is particularly advantageous because diabetics are highly susceptible to hyperlipidemia. Hulin, in U.S. Patent No. 5,306,726, claimed phenylpropionic acid derivatives and disclosed compounds that had hypoglycemic and hypocholesterolemic
15 activity useful for the treatment of diabetes and atherosclerosis. Miyata, et al. found a class of phosphonic diester derivatives useful for treating diabetes and hyperlipidemia (WO 93/23409). Hypolipidemic amino acid derivatives were disclosed in JA-028189.
20 Highly substituted aryl ethers of tyrosine were reported to have hypocholesterolemic activity (*J. Med. Chem.*, 38:695-707, 1995). No alkyl ethers of tyrosine were disclosed.

25 Pyrazole compounds have been shown to have hypoglycemic effect. For example, U.S. Patent. 5,183,825 issued February 2, 1993 disclosed the use of 4-Arylmethyl-5-alkyl-3H-pyrazol-3-ones as hyperlipidemia.

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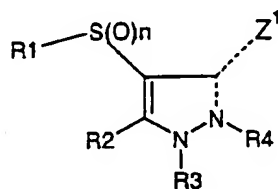
SUMMARY OF THE INVENTION

The present invention provides novel pyrazolones and pyrazolines useful in the treatment of hyperglycemia and/or hyperglycemia.

The present invention is also a method of use of novel pyrazolones and/or pyrazolines in the treatment of hyperlipidemia and/or hyperglycemia.

The present invention also provides a pharmaceutical composition containing a pyrazolone and/or pyrazoline compound of the invention useful for the treatment of non-insulin dependent diabetes mellitus (NIDDM).

The present invention provides novel compounds having utility as hypoglycemic and hypolipidemic agents of formula I;



I

wherein:

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R¹, R², R³, and R⁴ are independently alkyl, aryl aralkyl, heteroaryl, heteroalkyl fragments of 1-20 atoms (including, but not limited to, carbon, hydrogen, oxygen, nitrogen, sulfur, phosphorus, halogen) with or without substituents; Z¹ is variously hydrogen, oxygen, sulfur, nitrogen;
The dashed bonds are variously single or double;
n is an integer from zero to 2.

10

DEFINITIONS

The terms used to describe the instant invention have the following meanings herein.

A "mammal" is an individual animal that is a member of the taxonomic class mammalia. The class mammalia includes humans, monkeys, chimpanzees, gorillas, cattle, swine, horses, sheep, dogs, cats, mice, and rats.

"C₁₋₄ alkyl" refers to a straight or branched alkyl radicals having 1 to 4 carbon atoms, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, or t-butyl.

"C₁₋₄ alkoxy" refers to a straight or branched chain alkyl radicals attached to oxygen having 1 to 4 carbon atoms, for example, methoxy, ethoxy, n-propoxy, isopropoxy, or t-butoxy, and the like.

The terms "active ingredient" and "active compound" as used herein are synonymous and refer to a compound(s)

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of the present invention as represented by formula I or its pharmaceutically acceptable salts or prodrug individually contained or combined with other compound(s) of formula I in a formulation of the invention.

5

The term "aralkyl" refers to an aryl (C₁-C₆-alkyl) group.

The term "aryl" refers to a substituted or unsubstituted aromatic or heteroaromatic radical (wherein the terms "aromatic group" and "heteroaromatic group" refer to common aromatic rings having $4n + 2$ pi electrons in a monocyclic or bicyclic conjugated system) selected from the group consisting of 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 1-naphthyl, 2-naphthyl, 2-benzofuryl, 3-benzofuryl, 4-benzofuryl, 5-benzofuryl, 6-benzofuryl, 7-benzofuryl, 2-benzothiényl, 3-benzothiényl, 4-benzothiényl, 5-benzothiényl, 6-benzothiényl, 7-benzothiényl, 1-indolyl, 2-indolyl, 3-indolyl, 4-indolyl, 5-indolyl, 6-indolyl and 7-indolyl. Aryl groups may be optionally substituted at one or two carbon atoms of the aryl group, and may be with C₁-4 alkyl, C₁-4 alkoxy, halogen, -NO₂, -CN, -COOH, -CONH₂, -SO₃H, -SO₂NH₂ or trifluoromethyl. Examples of substituted aryl groups are 4-methyl-3-furyl, 3,4-dimethyl-2-thienyl, 2,4-dimethyl-3-thienyl, 3-ethoxy-4-methyl-2-benzofuryl, 2-cyano-3-benzofuryl, 4-trifluoromethyl-2-benzothiényl, 2-chloro-3-benzothiényl, 3,4-dichloro-2-pyridyl, 2-bromo-3-pyridyl, 2-fluoro-4-pyridyl, 4-fluoro-2-furyl, 2-carboxyphenyl, 4-carboxamidophenyl, 3-trifluoromethylphenyl, 2-bromo-1-naphthyl, 2,3-dimethyl-1-naphthyl, 3-carboxy-2-naphthyl, 5-carboxy-8-chloro-1-naphthyl, 3-ethyl-2-furyl, 8-fluoro-

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2-naphthyl, 5-trifluoromethyl-2-naphthyl, 6-ethoxy-2-naphthyl, 6,7-dimethoxy-2-naphthyl, 3-carboxy-2-naphthyl, and the like.

5 The term, "alkyl" by itself or as part of another substituent means, unless otherwise defined, a straight or branched chain monovalent hydrocarbon radical such as methyl, ethyl, n-propyl, isopropyl, n-butyl, tertiary butyl, isobutyl, sec-butyl, n-pentyl, and n-
10 hexyl.

 The term, "alkenyl" employed alone or in combination with other terms means a straight chain or branched monovalent hydrocarbon group having the stated
15 number range of carbon atoms, and typified by groups such as vinyl, propenyl, crotonyl, isopentenyl, and various butenyl isomers.

 The term, "hydrocarbyl" means an organic group
20 containing only carbon and hydrogen.

 The term, "halo" means fluoro, chloro, bromo, or iodo. The term, "heterocyclic radical", refers to radicals derived from monocyclic or polycyclic, saturated
25 or unsaturated, substituted or unsubstituted heterocyclic nuclei having 5 to 14 ring atoms and containing from 1 to 3 hetero atoms selected from the group consisting of nitrogen, oxygen or sulfur. Typical heterocyclic radicals are pyrrolyl, furanyl, thiophenyl, pyrazolyl,
30 imidazolyl, triazolyl, isoxazolyl, oxazolyl, thiazolyl, thiadiazolyl, indolyl, carbazolyl, norharmanyl, azaindolyl, benzofuranyl, dibenzofuranyl, thianaphthenyl, dibenzothiophenyl, indazolyl, imidazo[1.2-a]pyridinyl, benzotriazolyl, anthranilyl,

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1,2-benzoxazolyl, benzoxazolyl, benzothiazolyl, purinyl, pyridinyl, dipyridyl, pyrimidinyl, pyrazinyl, 1,3,5-triazinyl, quinolinyl, phthalazinyl, quinazolinyl, and quinoxalinyl.

5

The terms "alkylheterocyclic" and "arylheterocyclic" refer to radicals formed respectively by the bonding of a substituted or unsubstituted alkyl radical or aryl radical to a heterocyclic radical such that a new radical is generated with the reactive terminus at the alkyl or aryl group respectively.

The term "amino protecting group" as used herein refers to substituents of the amino group commonly employed to block or protect the amino functionality while reaction(s) are carried out at other functional groups of the compound. Examples of such amino-protecting groups include the formyl group, the phthalimido group, the trichloroacetyl group, the chloroacetyl, bromoacetyl and iodoacetyl groups, urethane-type blocking groups such as benzyloxycarbonyl, 4-phenylbenzyloxycarbonyl, 2-methylbenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 4-fluorobenzyloxycarbonyl, 4-chlorobenzyloxycarbonyl, 3-chlorobenzyloxycarbonyl, 2-chlorobenzyloxycarbonyl, 2,4-dichlorobenzyloxycarbonyl, 4-bromobenzyloxycarbonyl, 3-bromobenzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 4-cyanobenzyloxycarbonyl, 2-(4-xenyl)iso-propoxycarbonyl, 1,1-diphenyleth-1-yloxycarbonyl, 1,1-diphenylprop-1-yloxycarbonyl, 2-phenylprop-2-yloxycarbonyl, 2-(p-toluy)prop-2-yloxycarbonyl, cyclopentanyloxycarbonyl, 1-methylcyclopentanyloxycarbonyl, cyclohexanyloxycarbonyl, 1-methylcyclohexanyloxycarbonyl, 2-methylcyclohexanyloxycarbonyl, 2-(4-

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toluylsulfonyl)ethoxycarbonyl, 2-
(methylsulfonyl)ethoxycarbonyl, 2-
(triphenylphosphino)ethoxycarbonyl, 9-
fluorenylmethoxycarbonyl ("Fmoc"), 2-
5 (trimethylsilyl)ethoxycarbonyl, allyloxycarbonyl, 1-
(trimethylsilylmethyl)prop-1-en-3-yloxycarbonyl, 5-
benzisoxalylmethoxycarbonyl, 4-acetoxybenzyloxycarbonyl,
2,2,2-trichloroethoxycarbonyl, 2-ethynyl-2-
propoxycarbonyl, cyclopropylmethoxycarbonyl, 4-
10 (decyloxy)benzyloxycarbonyl, isobornyloxycarbonyl, 1-
piperidyloxycarbonyl, and the like; the
benzoylmethylsulfonyl, the 2-(nitro)phenylsulfenyl group,
the diphenylphosphine oxide group and like amino
protecting groups. The species of amino protecting group
15 employed is not critical so long as the derivatized amino
group is stable to the conditions of subsequent
reaction(s) on other positions of the molecule and can be
removed at the appropriate point without disrupting the
remainder of the molecule. Similar amino protecting
20 groups used in the cephalosporin, penicillin, and peptide
arts are also embraced by the above terms. Further
examples of groups referred to by the above terms are
described by J.S. Barton, "Protective Groups in Organic
Chemistry", J.G.W. McOmie, Ed., Plenum Press, New York,
25 N.Y., 1973, Chapter 2, and T.W. Greene, "Protective
Groups in Organic Synthesis", John Wiley and Sons, New
York, N.Y., 1981, Chapter 7 and T.W. Greene, "Protective
Groups in Organic Synthesis", 2nd Ed., John Wiley and
Sons, New York, N.Y., 1991. The related term "protected
30 amino" defines an amino group substituted with an amino
protecting group discussed above.

The term "carboxy protecting group" as used herein
refers to one of the ester derivatives of the carboxylic

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acid group commonly employed to block or protect the carboxylic acid group while reactions are carried out on other functional groups of the compound. Examples of such carboxylic acid protecting groups include benzyl, 4-nitrobenzyl, 4-methoxybenzyl, 3,4-dimethoxybenzyl, 2,4-dimethoxybenzyl, 2,4,6-trimethoxybenzyl, pentamethylbenzyl, 3,4-methylenedioxybenzyl, benzyhydryl, 4,4'-dimethoxybenzhydryl, 2,2,4,4'-tetramethoxybenzhydryl, t-butyl, isobutyl, n-butyl, propyl, isopropyl, ethyl, methyl, t-amyl, trityl, 4-methoxytrityl, 4,4'-dimethoxytrityl, 4,4',4'-trimethoxytrityl, trimethylsilyl, t-butyldimethylsilyl, phenylacyl, 2,2,2-trichloroethyl, p-toluenesulfonylethyl, 4-nitrobenzylsulfonylethyl, allyl, cinnamyl, or 1-(trimethylsilylmethyl)prop-1-en-3-yl, and like moieties. The species of carboxy-protecting group employed is not critical so long as the derivatized carboxylic acid is stable to the conditions of subsequent reaction(s) on other positions of the molecule and can be removed at the appropriate point without disrupting the remainder of the molecule. Carboxy protecting groups similar to those used in the cephalosporin, penicillin, and peptide arts can also be used to protect a carboxy group substituent of the compounds provided herein. Further examples of these groups are found in E. Haslam, "Protective Groups in Organic Chemistry", J.G.W. McOmie, Ed., Plenum Press, New York, N.Y., 1981, Chapter 5 and T.W. Greene, "Protective Groups in Organic Synthesis", 2nd Ed., John Wiley and Sons, New York, N.Y., 1991, Chapter 5.

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The term "prodrugs" as used herein defines derivatives of the compounds of the invention which have chemically or metabolically cleavable groups and become by solvolysis or under physiological conditions the

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compounds of the invention which are pharmaceutically active in vivo. Derivatives of the compounds of this invention have activity in both their acid and base derivative forms, but the acid derivative form often offers advantages of solubility, tissue compatibility, or delayed release in a mammalian organism (see, Bundgard, H., Design of Prodrugs, pp. 7-9, 21-24, Elsevier, Amsterdam 1985). Prodrugs include acid derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acidic compound with a suitable alcohol, or amides prepared by reaction of the parent acid compound with a suitable amine. Simple aliphatic or aromatic esters derived from acidic groups pendent on the compounds of this invention are preferred prodrugs. In some cases it is desirable to prepare double ester type prodrugs such as (acyloxy) alkyl esters or ((alkoxycarbonyl)oxy)alkyl esters. Particularly preferred esters as prodrugs are methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert-butyl, and morpholinoethyl.

The term "hydroxy activation agent" refers to acid halides, and acid anhydrides that are capable of converting a hydroxyl group into a leaving group labile to base treatment or nucleophilic displacement. Typical hydroxy activation agents include, but are not limited to sulfonating agents such as, methane sulfonyl chloride, p-toluenesulfonyl chloride, phenylsulfonyl chloride, trifluoromethylsulfonyl chloride, and the like, acylating agents such as isobutyl chloroformate, acetyl chloride, and the like, and halogenating reagents such as thionyl chloride, phosphorus tribromide, and the like.

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The term "activated hydroxy group" refers to the moiety that results when a compound containing a hydroxy group is reacted with a hydroxy activating reagent e.g. the transformation from O-H to o-methylsulfonyl, o,p-tolunesulfonyl, o-phenylsulfonyl, o-trifluoromethylsulfonyl, o-isobutylacetyl, o-acetyl, chloro, or bromo.

10 "Therapeutically effective amount" means that amount of a compound that will elicit the biological or medical response of a tissue, system, or mammal that is being sought by a researcher or clinician.

15 "Pharmaceutically acceptable salt" refers to a salt of the compound of formula I, which is substantially non-toxic to mammals. Typical pharmaceutically acceptable salts include those salts prepared by reaction of the compounds of the present invention with a mineral or
20 organic acid or an organic or inorganic base. Such salts are known as acid addition and base addition salts, respectively. It should be recognized that the particular counter-ion forming a part of any salt of this invention is not of a critical nature, so long as the
25 salt as a whole is pharmaceutically acceptable and as long as the counter-ion does not contribute undesired qualities to the salt as a whole.

Acids commonly employed to form acid addition salts
30 are inorganic acids such as, without limitation, hydrochloric acid, hydrobromic acid, hydriodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids, such as, without limitation, p-toluenesulfonic acid, methanesulfonic acid, oxalic acid, p-

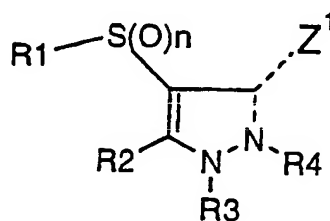
-13-

bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid, and the like.

5 Detailed Description of the Invention

The present invention provides novel compounds having utility as hypoglycemic and hypolipidemic agents of formula I;

10



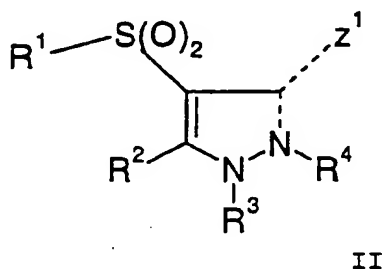
wherein:

15 R¹, R², R³, and R⁴ are independently alkyl, aryl, aralkyl, heteroaryl, heteroalkyl radicals of 1-20 atoms (including, but not limited to, carbon, hydrogen, oxygen, nitrogen, sulfur, phosphorus, halogen) with or without alkyl, aryl, aralkyl or heterocyclic radical substituents; Z¹ is independently selected from Hydrogen, 20 oxygen, sulfur, or nitrogen; the dashed bond is a single or double bond; and

n is an integer from zero to 2 or a salt or prodrug thereof.

PREFERRED COMPOUND OF THE INVENTION

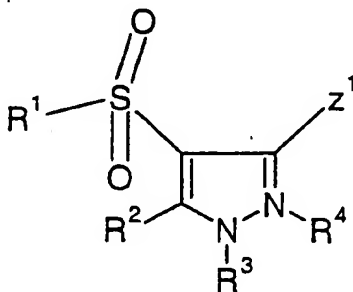
Preferred for the purpose of the present invention is a
5 compound of formula II:



wherein:

10 R^1 , R^2 , R^3 , and R^4 are as described above, and Z^1 is oxygen, sulfur, nitrogen or hydrogen connected by a single or double bond to form the carbonyl ($C=O$), thiocarbonyl ($C=S$), hydroxy (OH), thiol (SH) or amino (NH_2) functional groups.

15 More preferred is a compound selected from the group of compounds depicted by formula III:



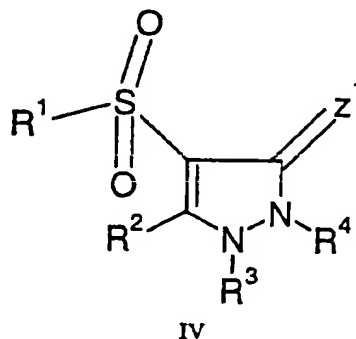
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III

wherein:

R¹, R², Z¹ are as described above and R³, R⁴ are
5 Hydrogen.

Most preferred is a compound of formula IV



10

wherein;

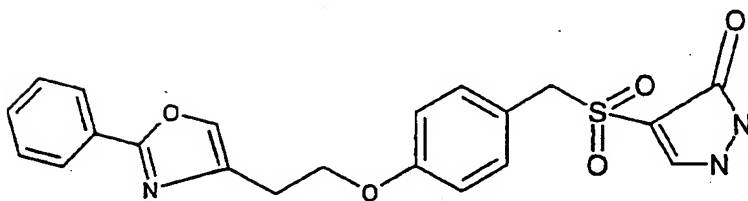
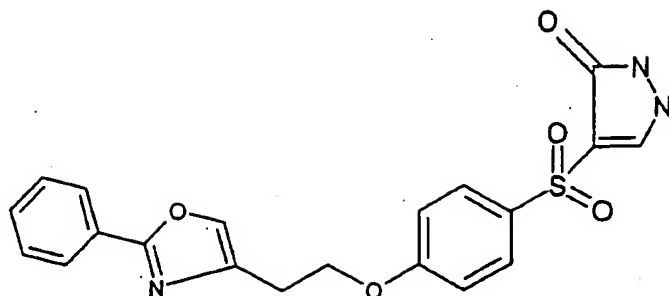
R², R³ and R⁴ are hydrogen; and

Z¹ is oxygen, NR⁵ or S, wherein R₅ is selected from the
group consisting of H, C₁-C₄ alkyl, phenyl or benzyl.

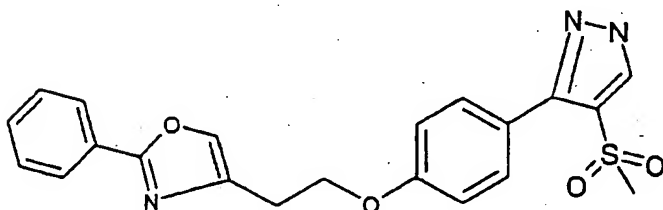
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Exemplary of preferred compounds for the present
invention is a compound selected from the group
consisting of:

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and



5

Pharmaceutically acceptable acid addition salts of the compounds of formula I are also aspects of this invention. Examples of such pharmaceutically acceptable salts are, without limitation, the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caproate, heptanoate, propiolate,

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oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methoxybenzoate, phthalate, sulfonate, xylenesulfonate, phenylacetate, 5 phenylpropionate, phenylbutyrate, citrate, lactate, -hydroxybutyrate, glycollate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate, and the like salts of the compound of formula I. The preferred acid addition salts are 10 those formed with mineral acids, such as, without limitation, hydrochloric acid, and hydrobromic acid, and those formed with organic acids, such as, without limitation, maleic acid and methanesulfonic acid.

15 Exemplary of compounds of formula I useful for the purposes of this invention include:

4 -(4-[2-(2-Phenyl-4-oxazolyl)ethoxy]phenylsulfonyl)-1H,2H-prazolin-3-one; 4 -(4-[2-(2-Phenyl-4-oxazolyl)ethoxy]phenylmethylsulfonyl)-1H,2H-prazolin-3-one; 3-(4-(2-Phenyl-4-oxazolyl)ethoxy)phenyl-4-methylsulfonyl-1H-1,2-pyrazoline; 2-Naphthylsulfonyl-pyrazolin-3-one; and 6-(2-Fluorobenzyloxy)-2-naphthylsulfonyl-pyrazolin-3-one. 20

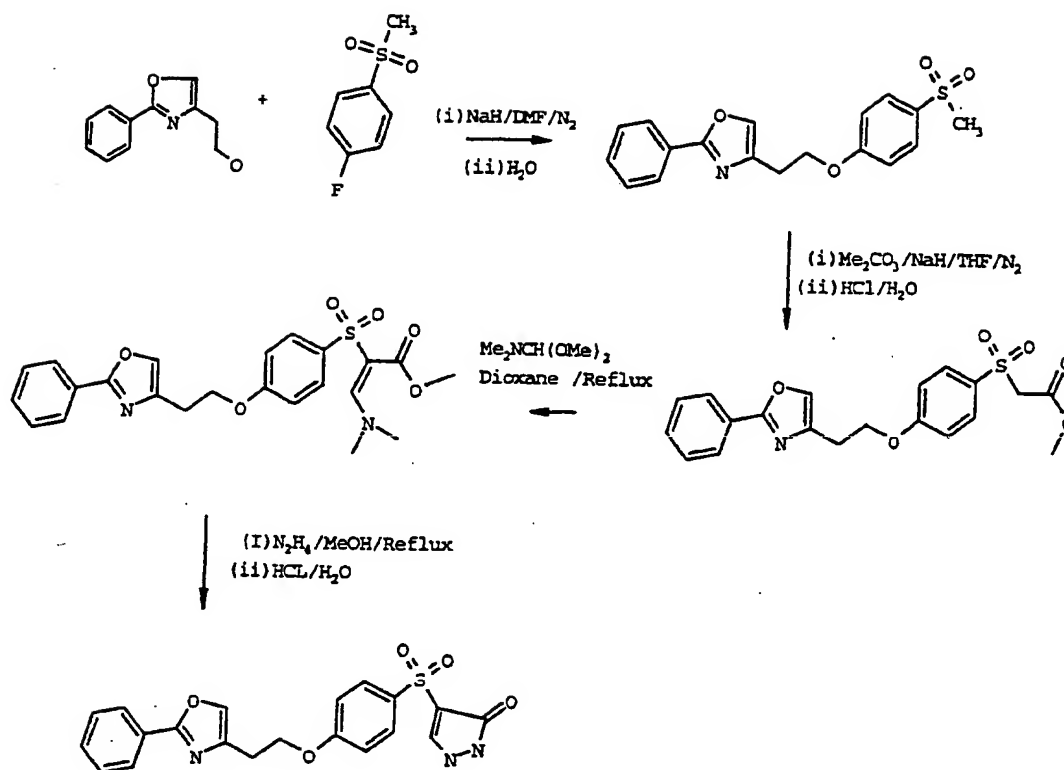
25 Compounds of Formula I are readily prepared by standard chemical reactions generally known to skilled practitioners and are summarized in standard texts and reference works; e.g. and i.a.: March, Advanced Organic Chemistry, Wiley-Interscience, New York 1985; Katritzky, 30 Handbook of Heterocyclic Chemistry, Pergamon Press, London 1985, Fieser and Fieser, Reagents for Organic Synthesis, Wiley Interscience, New York, 1968-1998

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Additional useful references are contained in "General methods for the acylation of sulfones", M. W. Thomasen, B. M. Handwerker, S. A. Katz, R. B. Belser, J. Org. Chem. 1988, 53, 906-907; N. N. Girotra, et.al., J. Med. Chem. 1992, 35, 3474-3482. For Example, Scheme I depicts the preparation of a typical candidate compound of the present invention by a sequence involving, first, nucleophilic displacement of an activated aromatic fluoride by an alkoxide (generated from an alcohol using a strong base such as sodium hydride and the like, in an indifferent solvent such as DMF) [March, pp 576-607], then acylation of the resulting sulfone (under the influence of a strong base such as sodium hydride and the like, in an indifferent solvent such as THF and the like) to produce a beta-sulfonyl ester. Subsequent condensation of the sulfonyl ester with a formamide acetal, such as DMA in a typical inert solvent such as THF at a moderately elevated temperature such as 50-60°C [Fieser and Fieser, 3, 115] produces a substituted acrylate ester which cyclizes upon treatment with a diatomic nucleophile such as hydrazine to produce a heterocyclic compound such as a pyrazolin-3-one.

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Scheme 1

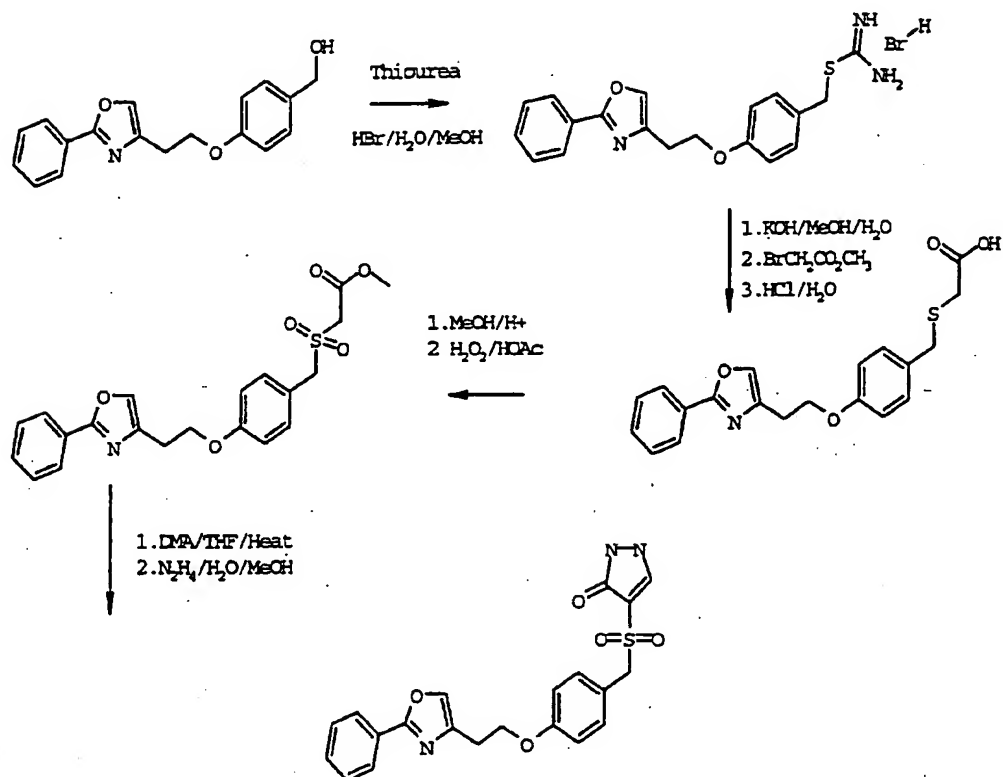


- 5 An alternate route to compounds of the present
 invention is depicted in Scheme 2, wherein the
 intermediate beta sulfonyl esters are secured by a
 sequence involving conversion of an alcohol to an
 isothiuronium salt by reaction with thiourea and a
 10 hydrohalic acid such as HBr in a convenient solvent
 mixture such as water/methanol, hydrolysis of the
 isothiuronium halide to a thiol (which may or may not be
 isolated), and alkylation of the thiol with a substituted
 acid derivative such as methyl bromoacetate [Fieser, 1,
 15 1165]. Subsequent oxidation of the resulting thio-oxy

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acid derivative with a reagent such as hydrogen peroxide affords a beta sulfonyl ester, used as described above.

Scheme 2



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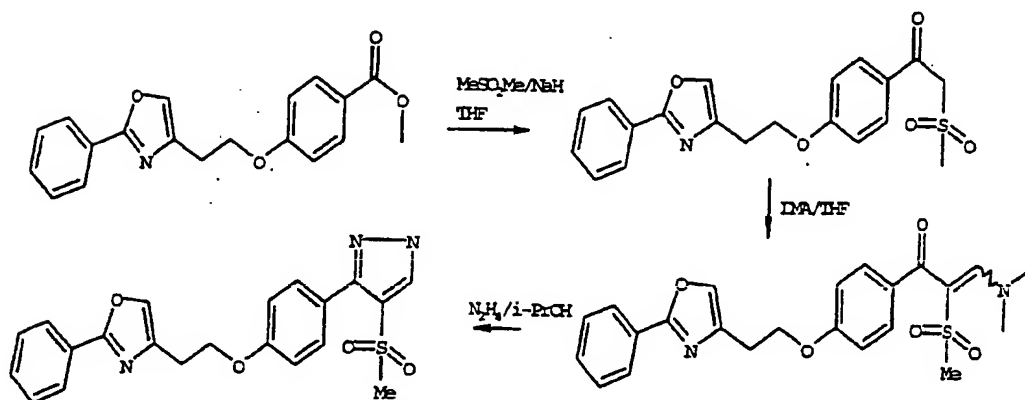
An example of the synthesis of candidate pyrazolines is depicted in Scheme 3, wherein a beta sulfonyl ketone is produced by the alkylation of an ester, such as a substituted benzoate, with an alkyl sulfone, such as dimethyl sulfone in the presence of a base such as sodium hydride in an indifferent solvent such as THF, at a convenient temperature such as 50-60°C. Condensation of the sulfonyl ketone with a reagent such as DMA produces a substituted vinyl keto sulfone, which undergoes

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cyclization to a heterocycle such as a pyrazoline upon treatment with a diatomic nucleophile such as hydrazine.

5

Scheme 3

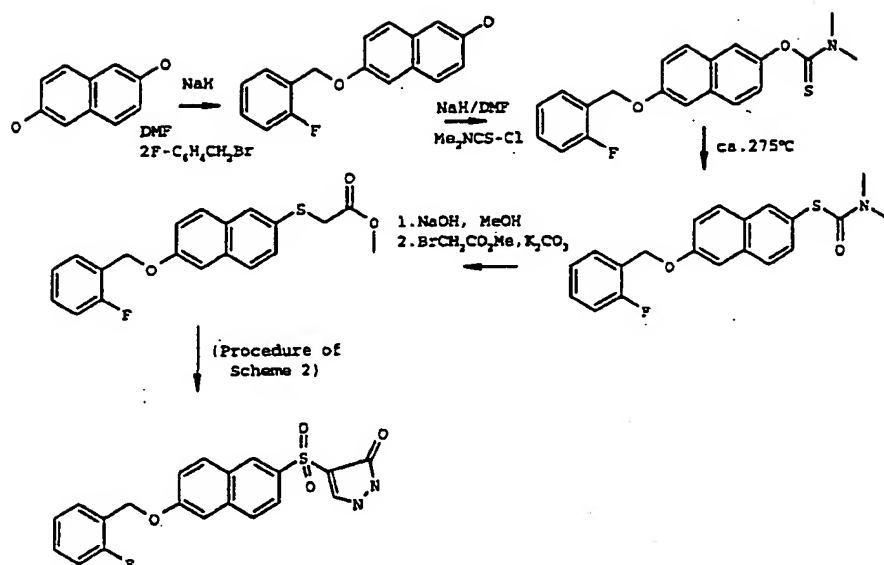


Aromatic phenols (including e.g., naphthols) may be
 10 used to produce candidate compounds of the present
 invention as illustrated in Scheme 4, wherein a
 substituted naphthol is converted to an aryl thioacetic
 acid derivative by means of a Newman Rearrangement
 [Fieser 2, 173]. Subsequent conversion to a pyrazolin-3-
 15 one then follows Scheme 2. The sequence may be carried
 out without purification of intermediates (cf Example 4)
 or by isolation and characterization of intermediates (cf
 Example 5).

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Scheme 4



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Formulation

The compounds of the present invention can be administered in oral forms, such as tablets, capsules, pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. They may also be administered in parenteral forms, such as intravenous (bolus or infusion), intraperitoneal, subcutaneous, intramuscular, and the like forms, well known to those of ordinary skill in the pharmaceutical arts. The compounds of the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using transdermal delivery systems well-known to those of ordinary skill in that art.

20

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A dosage regimen utilizing the compounds of the present invention is selected by one of ordinary skill in the medical or veterinary arts in view of a variety of factors, including without limitation, the species, age, weight, sex, and medical condition of the recipient, the severity of the condition to be treated, the route of administration, the level of metabolic and excretory function of the recipient, the dosage form employed, the particular compound and salt thereof employed, and the like.

The compounds of the present invention are preferably formulated prior to administration together with one or more pharmaceutically acceptable excipients. Excipients are inert substances such as, without limitation, carriers, diluents, flavoring agents, sweeteners, lubricants, solubilizers, suspending agents, binders, tablet disintegrating agents and encapsulating material.

Therefore, yet another embodiment of the present invention is a pharmaceutical formulation comprising a compound of the invention and one or more pharmaceutically acceptable excipients that are compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. Pharmaceutical formulations of the invention are prepared by combining (e.g., mixing) a therapeutically effective amount of the compounds of the invention together with one or more pharmaceutically acceptable excipients therefor. In making the compositions of the present invention, the active ingredient may be admixed with a diluent, or enclosed within a carrier, which may be in the form of a capsule, sachet, paper, or other container.

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The carrier may serve as a diluent, which may be solid, semi-solid, or liquid material which acts as a vehicle, or can be in the form of tablets, pills, powders, lozenges, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments, containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders.

10

For oral administration in the form of a tablet or capsule, the active ingredient may be combined with an oral, non-toxic, pharmaceutically acceptable carrier, such as without limitation, lactose, starch, sucrose, glucose, methyl cellulose, calcium carbonate, calcium phosphate, calcium sulfate, sodium carbonate, mannitol, sorbitol and the like; together with, optionally, disintegrating agents, such as, without limitation, maize, starch, methyl cellulose, agar, bentonite, xanthan gum, alginic acid, and the like; and optionally, binding agents, for example, without limitation, gelatin, acacia, natural sugars, beta-lactose, corn sweeteners, natural and synthetic gums, acacia, tragacanth, sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like; and optionally, lubricating agents, for example, without limitation, magnesium stearate, sodium stearate, stearic acid, sodium oleate, sodium benzoate, sodium acetate, sodium chloride, talc, and the like.

30

In powders, the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary binding properties in suitable proportions and compacted in the shape and size

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desired. The powders and tablets preferably contain from about 1 to about 99 weight percent of the active ingredient which is the novel composition of the instant invention. Suitable solid carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, 5 pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethyl cellulose, low melting waxes, and cocoa butter.

10 Sterile liquid formulations include suspensions, emulsions, syrups, and elixirs. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable carrier, such as sterile water, sterile organic solvent, or a mixture of both sterile water and 15 sterile organic solvent.

The active ingredient can also be dissolved in a suitable organic solvent, for example, aqueous propylene glycol. Other compositions can be made by dispersing the 20 finely divided active ingredient in aqueous starch or sodium carboxymethyl cellulose solution or in a suitable oil.

Preferably, the pharmaceutical formulation is in 25 unit dosage form. A "unit dosage form" is a physically discrete unit containing a unit dose, suitable for administration in human subjects or other mammals. A unit dosage form can be a capsule or tablet, or a number of capsules or tablets. A "unit dose" is a predetermined 30 quantity of the active compound of the present invention, calculated to produce the desired therapeutic effect, in association with one or more pharmaceutically acceptable excipients. The quantity of active ingredient in a unit dose may be varied or adjusted from about 0.1 to about

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1000 milligrams or more according to the particular treatment involved. It may be appreciated that it may be necessary to make routine variations to the dosage depending on the age and condition of the recipient. The
5 dosage will also depend on the route of administration.

The oral route is most preferred. Typical oral dosages of the present invention, when used for the indicated effects, will range from about 0.01 mg per kg
10 body weight per day (mg/kg/day) to about 50 mg/kg/day, preferably from 0.1 mg/kg/day to 30 mg/kg/day, and most preferably from about 0.5 mg/kg/day to about 10
mg/kg/day. The compounds of the present invention may be administered in a single daily dose, or the total daily
15 dose may be administered in divided doses, two, three, or more times per day. Where delivery is via transdermal forms, of course, administration is continuous.

The human to whom the compounds and formulations of
20 the present invention are administered is afflicted with a disease or condition in which blood glucose levels are not adequately controlled without medical intervention, but wherein there is endogenous insulin present in the human's blood and or afflicted with a disease or
25 condition wherein lipid levels are not adequately or desirably controlled as in hyperlipidemia. Non-insulin dependent diabetes mellitus (NIDDM) is a chronic disease or condition characterized by the presence of insulin in the blood, even at levels above normal, but resistance or
30 lack of sensitivity to insulin action at the tissues. The compounds and formulations of the present invention are also useful to treat acute or transient disorders in insulin sensitivity, such as sometimes occur following surgery, trauma, myocardial infarction, and the like.

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The compounds and formulations of the present invention are also useful for lowering serum triglyceride levels. Elevated triglyceride level, whether caused by genetic predisposition or by a high fat diet, is a risk factor for the development of heart disease, stroke, and circulatory system disorders and diseases. The physician of ordinary skill will know how to identify humans who will benefit from administration of the compounds and formulations of the present invention.

The following formulation examples are illustrative only and are not intended to limit the scope of the invention in any way.

15

Formulation 1

Hard gelatin capsules are prepared by mixing the following ingredients and filling the mixture, in 460 mg quantities, into hard gelatin capsules.

20

Ingredient	Quantity (mg/capsule)
Active ingredient	250
Starch, dried	200
Magnesium stearate	10
Total	460

Formulation 2

A tablet containing 250 mg of the compound of the present invention is prepared by blending the components

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listed below and then compressing 665 mg of the blend into a tablet.

Ingredient	Quantity (mg/tablet)
Active ingredient	250
Cellulose, microcrystalline	400
Silicon Dioxide, fumed	10
Stearic Acid	5
Total	665

5

Formulation 3

A tablet containing 60 mg of the compound of the present invention is prepared as follows:

Ingredient	Quantity. (mg/tablet)
Active ingredient	60
Starch	45
Cellulose, microcrystalline	35
Polyvinylpyrrolidone, 10%, aqueous	4
Sodium carboxymethyl starch	4.5
Magnesium stearate	0.5
Talc	1
Total	150

10

The active ingredient, starch, and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders and then passed through

15

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a No. 14 mesh U.S. sieve. The granules so produced are dried at 50 °C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

10

Formulation 4

Capsules containing 80 mg of the active compound of the present invention are made as follows:

Ingredient	Quantity (mg/capsule)
Active ingredient	80
Starch	59
Cellulose, microcrystalline	59
Magnesium stearate	2
Total	200

15

The active ingredient, starch, cellulose, and magnesium stearate are blended, the blend is passed through a No. 45 mesh U.S. sieve, and then hard gelatin capsules are filled with 200 mg of the blend.

20

Formulation 5

Suppositories each containing 225 mg of active compound of the present invention are made as follows:

25

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Ingredient	Quantity (mg/suppository)
Active ingredient	225
Saturated fatty acid glycerides	2,000
Total	2,225

The active compound is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides, previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2 g capacity and allowed to cool.

Formulation 6

10 Suspensions each containing 50 mg of active compound of the present invention per 5 mL dose are made as follows:

Ingredient	Quantity per dose
Active ingredient	50 mg
Sodium Carboxymethyl Cellulose	50 mg
Syrup	1.25 mL
Benzoic Acid Solution	0.10 mL
Flavor	q.v.
Color	q.v.
Purified Water to total volume:	5 mL

15 The active ingredient, starch, cellulose, and magnesium stearate are blended, the blend is passed through a No. 45 mesh U.S. sieve, and then hard gelatin capsules are filled with 200 mg of the blend.

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Formulation 7

- 5 An intravenous formulation may be prepared as follows:

Ingredient	Quantity
Active ingredient	100 mg
Sterile, isotonic saline	1000 mL

- 10 The compound of the present invention is dissolved in the saline and administered intravenously at a rate of 1 mL per minute to a subject in need thereof.

Formulation 8

- 15 An aerosol solution is prepared by mixing the active ingredient with ethanol and then with the propellant 22, cooled to -30 °C, and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted with the remainder of the
20 propellant. The valve units are finally fitted to the container.

Ingredient	Weight %
Active ingredient	0.25
Ethanol	29.75
Propellant 22	70.00
Total	100.00

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Demonstration of Hypoglycemic Efficacy

Male obese-diabetic viable yellow (AVY) mice were divided into two groups of 6 each. One group was fed repelletized purina 5008 Chow and the second group was fed repelletized Purina 5008 Chow, admixed with varying doses of the candidate compound. Blood samples were taken before the experiment was initiated and 7 and 14 days after initiation. Body weight and food consumption were monitored. The blood glucose level after 7 or 14 days of treatment was measured and recorded as a percent of the initial value, compared to the untreated control (first) group. The results are presented in the table 1 below; and include the dose of the candidate compound as a weight percent of the amount incorporated into the diet. Also in the table is a representative value for a positive control (a known hypoglycemic agent as disclosed by T. Sohda, K. Mizuno, Y. Momose, H. Ikeda, T. Fujita, and K. Meguro, *J. Med. Chem.*, 1992, 35, 2617) administered in the same way as a candidate compound of the present invention.

Table 1

Example No.	Dose	%BG14 (BG0 = 100)
1	.03	32
2	.03	81
3	.01	72
4	.1	94
Takeda "Compound 17"	.003	29.0

25

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BG means blood glucose level; BG0 means blood glucose level at day zero and BG14 means blood glucose level at day 14 accordingly. Takeda "Compound 17" is disclosed by T. Sohda, K. Mizuno, Y. Momose, H. Ikeda, T. Fujita, and K. Meguro, *J. Med. Chem.*, 1992, 35, 2617.

Experimental-General

Melting points were measured using a Thomas Hoover capillary instrument and are uncorrected. Ratios are on a weight basis, except fluid mixtures for chromatography, which are on a volume basis. Temperatures are in degrees Celsius. Chromatography was performed on silica under low or medium pressure "flash" conditions as described by C. W. Still, et al., *J. Org. Chem.* 43:2923 (1978). Thin Layer Chromatography (TLC) was performed on glass plates coated with silica gel, 240 microns, grade 2.

Proton NMR spectra were obtained using at 300.15 MHz and peak positions are reported as delta values relative to an internal TMS standard.

Abbreviations

	g,	grams
25	THF,	Tetrahydrofuran
	DMF,	N,N-Dimethylformamide
	DMA,	N,N-Dimethylformamide Dimethyl Acetal
	NaH,	Sodium Hydride, a 60% (wt) dispersion in mineral oil
30	MSOH,	Methanesulfonic Acid
	mL,	Milliliter
	mM,	Millimole
	°C,	Degrees Centigrade

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i-PrOH, Isopropanol
MeOH, Methanol
Et₂O, Diethyl Ether
Mp, melting point
5 rt, ambient room temperature

EXAMPLES**Example 1**

10 4 - (4-[2-(2-Phenyl-4-oxazolyl)ethoxy]phenylsulfonyl)-
1H,2H-prazolin-3-one

(A) 4-[2-(2-Phenyl-4-oxazolyl)ethoxy]phenyl Methyl
Sulfone

15 A stirred solution of 2-(2-Phenyl-4-oxazolyl)ethanol
(12.6g, 66mM) in 20mL of DMF was blanketed with nitrogen
and treated with 1.95 g (48 mM) of NaH. Gas evolution
began followed by the precipitation of a solid. The
reaction was allowed to proceed for 5 minutes and treated
20 with 10 g (57 mM) of 4-fluorophenylmethyl sulfone. The
resulting frothy mixture was kept at 55-60 °C for 2.5h,
when TLC analysis demonstrated most of the starting
materials had been consumed. The mixture was cooled,
treated with ice and water and stirred. The resulting
25 precipitate was filtered and washed with water and
hexanes. Recrystallization of the solid from i-PrOH
provided 10.3 g (53%) of the product as glittering
flakes,
mp 147-149 °C.

30

Anal. Calcd. for C₁₈H₁₇NO₄S: (MW 343) C 62.96,
H 4.99, N 4.08
Found: C 63.16, H 4.91, N 4.29

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NMR(DMSO-d₆): 3.05(t, 2H), 3.10 (s, 3H), 4.40(t, 2H),
7.20(d, 2H), 7.55(m, 3H), 7.85(d, 2H), 7.95(m, 2H), 8.05
(s, 1H)

Mass Spec. m/e 344

5

(B) Methyl 4-[2-(2-Phenyl-4-oxazolyl)ethoxy]phenylsulfonyl]acetate.

A stirred solution of 4.5 g (13 mM) of the product
10 from part (A) above in 50 mL of THF was treated with 10
mL (excess) of dimethyl carbonate, followed by 1.97 g (49
mM) of NaH. The initial gas evolution was allowed to
subside and the mixture refluxed under nitrogen for 3h.
The cooled mixture was treated with ice, 5N HCl and
15 extracted with ethyl acetate. The extracts were washed
successively with water, 5% sodium bicarbonate, water,
brine and dried over magnesium Sulfate. Removal of
solvent afforded an oil which solidified on trituration
with hexanes. Recrystallization from methylene chloride-
20 Hexane provided 1.69 g (32.4%) of product as a white
powder mp 112-114 °C.

Anal. Cal for C₂₀H₁₉NO₆S (MW 401) C 59.84, H 4.77,
N 3.48, S, 7.99

25 Found. C 59.81, H 4.71, N 3.66, S 8.02

NMR(CDCl₃) 3.15(t, 2H), 3.60 (s, 3H), 4.15 (s, 2H),
4.45(t, 2H), 7.20(d, 2H), 7.55(m, 3H), 7.85(d, 2H), 7.95(m,
2H), 8.05(s, 1H)]

30 MS. m/e 401

IR(KBr) 1750cm⁻¹

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(C) (E/Z) Methyl 1-(4-[2-(2-Phenyl-4-oxazolyl)ethoxy]phenylsulfonyl)-2-N,N-dimethylamino Acrylate.

A stirred solution of 1.5 g (3.7 mM) of the compound prepared in (B) above in 20 mL of Dioxane was treated with 1.2 mL (9.0 mM) of DMA and heated to reflux 7h. The mixture was kept at rt overnight and then concentrated in vacuo. Trituration of the residue with Et₂O produced a solid which was recrystallized from MeOH to provide 1.10 g (64%) of product as nearly white crystals, mp 111-114 °C.

Anal. Cal. For C₂₃H₂₄N₂O₆S (MW 456) : C 60.51, H 5.30, N 6.14.

Found: C 60.58, H 5.29, N 6.09

NMR(CDCl₃) 2.95 (broad s, 3H), 3.15(t, 2H), 3.30 (broad s, 3H), 3.60 (s, 3H), 4.45(t, 2H), 7.20(d, 2H), 7.55 (m, 3H), 7.55, 7.85(d, 2H), 7.95(m, 2H), 8.05(s, 1H)

MS (FD+) m/e 456

IR(KBr) 1609, 1614, 1590 cm⁻¹

(D) 4-(4-[2-(2-Phenyl-4-oxazolyl)ethoxy]phenylsulfonyl)-1H,2H-prazolin-3-one.

A stirred mixture of 7.79 g (17.0 mM) of the intermediate prepared according to (C) above in 40mL of MeOH was treated with 12 mL of 80% Hydrazine Hydrate and heated to reflux for 3h. The resulting clear solution was partially concentrated, diluted with water and acidified to pH 2-3. The precipitate which formed overnight was collected by filtration, washed with water and recrystallized from THF/MeOH to provide 5.70 g (81%)

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of the product as fine white crystals mp 195-200 °C
(dec.)

Anal. Cal. For C₂₀H₁₇N₃O₅S (MW 411) : C 58.39, H 4.17,
5 N 10.21.

Found: C 58.58, H 4.36, N 10.02.

NMR (DMSO-d₆) 3.05 (t, 2H), 3.4 (b. s., 2H, exchanges with
D₂O), 4.40 (t, 2H), 7.20 (d, 2H), 7.55 (m, 3H), 7.85 (d, 2H),
7.95 (m, 2H), 8.05 (s, 1H)]

10

Example 2

4 -(4-[2-(2-Phenyl-4-
oxazolyl)ethoxy]phenylmethylsulfonyl)-1H,2H-prazolin
15 -3-one.

(A) S- 4-[2-(2-Phenyl-4-oxazolyl)ethoxy]phenylmethyl Isothiuronium Bromide.

A stirred mixture of 7.2 g (24 mM) of 4-[2-(Phenyl-
20 4-oxazolyl)phenylmethanol, 2.75 g (36 mM) thiourrea and
75 mL of MeOH was treated with 7 mL of 48% HBr. The
resulting clear solution was heated to reflux 3h and then
kept at room temperature for 8 to 16 hours overnight.
The solution was diluted with 100 mL iPrOH, concentrated
25 to about half volume and cooled. The solid which formed
was removed by filtration and washed with cold iPrOH.
Recrystallization from iPrOH provided 8.62 g (81%) of
product as a white solid mp 197-200 °C dec.

30 Anal. Cal. For C₁₉H₁₉N₃O₂S. HBr (MW 434): C 52.54,
H 4.64, N 9.67.

Found: C 52.38, H 4.71, N 9.51.

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NMR: 3.05(t, 2H), 4.40(t, 2H), 4.35 (s, 2H), 7.20(d, 2H), 7.55(m, 3H), 7.6 (s, 1H), 7.85(d, 2H), 7.95(m, 2H), 8.9-9.2(broad, 3H).

IR: 3104 (broad), 1657, 1589, 1550, 1515 cm⁻¹

5

(B) Methyl S-(4-[2-(2-Phenyl-4-oxazolyl)ethoxy]phenylmethyl)sulfonylacetate

To a stirred solution of 4.5 g of 85% KOH (65.9 mM KOH) in 50 mL of MeOH was added 4.3 g (10 mM) of the
10 intermediate prepared in part (A) above. The resulting mixture was heated to reflux under nitrogen for 4h, during which time most of the solids had gone into solution. The cooled mixture was stirred under nitrogen for 8 to 16 hours and treated with 0.6 g of powdered KI
15 and 2.0 mL of methyl bromoacetate. The resulting mixture was maintained under nitrogen at ambient temperature for 24h then treated with ice and 5N HCL. The mixture was extracted with ethyl acetate and the extracts washed successively with water and brine. The extracts were
20 dried with magnesium sulfate and the solvent removed in vacuo to provide a white powder. Trituration of the residue with Et₂O/Hexane provided 2.70 g of white crystals, mp 102-104 °C. The solid was dissolved in 50 mL of MeOH, the solution treated with 0.2 mL of
25 methanesulfonic acid and refluxed for 6h. The bulk of the solvent was removed by distillation and the residual syrup dissolved in ethyl acetate. The ethyl acetate solution was washed successively with water, 5% sodium bicarbonate, water, brine and dried with magnesium
30 sulfate. The solvent was removed and the residual oil stirred with 15 mL of HOAc. 4 mL of 30% hydrogen peroxide was added and the mixture stirred at ambient

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temperature for 8 to 16 hours. The mixture was diluted with water and extracted with ethyl acetate. The ethyl acetate extracts were washed successively with water, 5% sodium bicarbonate, water, brine and dried with magnesium sulfate. Removal of the solvent and recrystallization of the residue from methylene chloride-Hexane provided 0.92 g (22%) of product as white crystals, mp 93-95 °C.

Anal. Cal. For $C_{21}H_{21}NO_6S$ (MW 415): C 60.71, H 5.09, N 3.37.

Found: C 61.01, H 5.21, N 3.30.

NMR: 3.05(t, 2H), 3.70 (s, 3H), 3.80 (s, 2H) 4.40(t, 2H), 4.45 (s, 2H), 6.90(d, 2H), 7.30 (d, 2H), 7.55(m, 3H), 7.6 (s, 1H), 7.95(m, 2H)

(C) 4 -(4-[2-(2-Phenyl-4-oxazolyl)ethoxy]phenylmethylsulfonyl)-1H,2H-prazolin-3-one.

A solution of 0.90 g (2.2 mM) of the intermediate from (B) above in 20mL of THF was treated with 0.7 mL (5 mM) of DMA and heated to reflux for 7h. The cooled solution was evaporated in vacuo and the residual oil washed with Et_2O . A solution of the residue in 20 mL of MeOH was treated with 1mL of 85% hydrazine hydrate and heated to reflux for 2h. The cooled solution was treated with 100 mL 1N HCL and allowed to stand at room temperature for 8 to 16 hours and the gummy solid which had formed was filtered and washed with H_2O .

Recrystallization from iPrOH provided 0.5 g (53%) of product as a white powder, m.p. 228-230 °C.

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Anal. Cal. For $C_{21}H_{19}N_3O_5S$ (MW 425): C 59.28, H 4.50,

N 9.88.

Found: C 59.28, H 4.53, N 9.86

MS m/e 425

5 NMR: 3.05(t, 2H), 4.40 (s, 2H) 4.38(t, 2H), 6.90(d, 2H),
7.30 (d, 2H), 7.55(m, 3H), 7.6 (s, 1H), 7.95(m,
2H), (xx.x, bs, exchange with D_2O 1h)

10 **Example 3**

3-(4-(2-Phenyl-4-oxazolyl)ethoxy)phenyl-4-methylsulfonyl-
1H-1,2-pyrazoline

(A) (4-(2-Phenyl-4-oxazolyl)ethoxy)phenyl Methylsulfonyl

15 **Methanone**

A stirred mixture of 6.23 g (19.2 mM) methyl 4-(2-phenyl-4-oxazolyl)ethoxybenzoate, 11.73 g (124 mM) dimethyl sulfone and 100 mL THF under Nitrogen was treated with 3.4 g (85 mM) of NaH). After the initial
20 gas evolution had subsided, the mixture was heated to reflux 4h, cooled and treated with ice. The mixture (pH ca. 12) was extracted with ethyl acetate. The EtOAc extracts were washed with H_2O , brine and dried over magnesium sulfate. Removal of solvent and trituration of
25 the residue with hexane provided a soft white powder. Recrystallization of the residue from THF/iPrOH afforded 4.60 g (62%) of product as white flakes mp 133-135 °C.

Anal. Cal. For $C_{20}H_{19}NO_5S$ (MW 385): C 62.32, H 4.97,

30 N 3.63.

Found: C 62.03, H 4.89, N 3.67.

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NMR 3.05(t, 2H), 3.10 (s, 3H) 4.40(t, 2H), 4.55 (s, 2H),
7.20(d, 2H), 7.55 (m, 3H), 7.85(d, 2H), 7.95(m, 2H),
8.05(s, 1H)]
MS: m/e 385.

5

(B) E/Z 1-[4-(2-Phenyl-4-oxazolyl)ethoxy)phenyl]-1-Methylsulfonyl-2-N,N-Dimethylamino Ethene.

A stirred solution of 1.06 g (2.7 mM) of the
10 intermediate prepared in part (A) above in 20 mL THF was
treated with 1.0 mL (7.5 mM) of DMA and heated to reflux
2h. The resulting brown solution was kept at room
temperature for 8 to 16 hours, refluxed an additional 8h
and then evaporated. Trituration of the gummy residue
15 with Et₂O produced a soft white powder.
Recrystallization from THF/i-PrOH afforded 1.14 g (95%)
of product as white flakes m.p. 143-154 °C.

Anal. Cal. For C₂₃H₂₄N₂O₅S (MW 440): C 62.71, H 5.49, N
20 6.36
Found: C 62.77, H 5.59, N 6.19
MS: m/e 440

(C) 3-(4-(2-Phenyl-4-oxazolyl)ethoxy)phenyl-4-methylsulfonyl-1H-1,2-pyrazoline

25 A stirred mixture of 1.10 g (2.5 mM) of the
intermediate prepared in part (B) above and 25 mL of i-
PrOH was treated with 1 mL of 85% Hydrazine Hydrate and
heated to reflux for 2h, during which time the initial
30 solid dissolved and was replaced by a new precipitate.
The resulting mixture was kept at room temperature for 8
to 16 hours and diluted with water. The solid formed was
removed by filtration, washed with H₂O and drained.

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Recrystallization from THF/i-PrOH afforded 0.88 g (86%) of product as a fluffy white powder, m.p. 185-187 °C.

Anal. Cal. For $C_{21}H_{19}N_3O_4S$ (MW 409): C 61.60, H 4.68,

5 N 10.26.

Found: C 61.55, H 4.70, N 10.14

MS: m/e 409

NMR (DMSO- d_6): 2.50 (d, 6H), 3.05 (t, 2H), 3.10 (s, 3H),
4.40 (t, 2H), 7.20 (d, 2H), 7.55 (m, 3H), 7.66 (m, 1H),

10 7.85 (d, 2H), 7.95 (m, 2H), 8.05 (s, 1H)]

(D) 3-(4-(2-Phenyl-4-oxazolyl)ethoxy)phenyl-4-methylsulfonyl-1H-1,2-pyrazoline

A stirred mixture of 0.88 g (2.0 mm) of the
15 intermediate prepared in part (B) in 20 mL of i-PrOH was treated with 2 mL of 80% Hydrazine Hydrate and heated to reflux 6h. After an additional 12h at room temperature, TLC demonstrated complete consumption of the reactant. The mixture was treated with H_2O , heated to boiling,
20 cooled and filtered. The white powder was washed with H_2O , boiled with i-PrOH, cooled and filtered. The residue was washed with Ether and dried to afford 0.55 g (67%) of product as fluffy white needles, mp. 187-189 °C.

25 Anal. Cal. For $C_{21}H_{19}N_3O_4S$ (MW 409): C 61.60, H 4.68,

N 10.26.

Found: C 61.55, H 4.70, N 10.14

MS: m/e 409

30

Example 4

(A) 2-Naphthylsulfonyl-pyrazolin-3-one

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A stirred mixture of 6.2 g (24.8 mM) of 2-naphthylthioacetic acid and 40 mL of MeOH was treated with three drops of MsOH and heated to reflux for 3h and then concentrated to ca. half volume. The cooled residue
5 was diluted with H₂O and extracted into EtOAc. The EtOAc extracts were washed with H₂O, 5% sodium bicarbonate, H₂O, brine and evaporated to a yellow brown oil. The residue was dissolved in 20 mL of HOAc and treated with 10 mL of 30% H₂O₂. The resulting solution was kept at
10 ambient temperature for 48h, diluted with H₂O and the resulting precipitate removed by filtration. The solid was washed thoroughly with H₂O and dried to produce a solid mp 73-75 °C. A solution of 2.64 g (10 mM) of the solid in 30 mL of EtOAc was treated with 2 mL (excess) of
15 DMA and heated to reflux for 3h. The resulting dark yellow brown solution was cooled and concentrated in vacuo to provide a dark gum which solidified to tan crystals mp 126-129 °C on trituration with cold MeOH. A stirred mixture of this solid and 40 mL of MeOH was
20 treated with 2 mL of 85% hydrazine hydrate and heated to reflux. The resulting solution was refluxed 3h, cooled and diluted with H₂O. the precipitate which formed was collected by filtration, washed with H₂O and dried to provide 0.92 g (33% overall) of product as fine white
25 crystals mp 239.5 °C (dec.)

Anal. Cal. For C₁₃H₁₀N₂O₃S (MW 274): C 56.93, H 3.68, N 10.21.

Found: C 57.23, H 3.90, N 9.93

30 MS: m/e 274

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Example 5**6-(2-Fluorobenzyloxy)-2-naphthylsulfonyl-pyrazolin-3-one****(A) 6-(2-Fluorobenzyloxy)-2-naphthol.**

5 A stirred solution of 15.0 g (94.0 mM) of 2,6-dihydroxynaphthalene in 60 mL of DMF was treated with 3.21 g (80.0 mM) of NaH under nitrogen. The resulting dark solution was treated dropwise with a solution of 5.94 g (31.0mM) of 2-fluorobenzyl bromide in 20 mL of
10 Et₂O over 0.75h. The mixture was stirred an additional 2h then treated cautiously with 200 mL 1N HCl. The mixture was stirred 8 to 16 hours then filtered. The solid was washed thoroughly with water and dried. Flash chromatography produced a solid which was recrystallized
15 from i-PrOH to afford 4.51 g (56%) of product as gray crystals mp 143-144 °C.

Anal. Cal. For C₁₇H₁₃FO₂ (MW 268): C 76.11, H 4.88.

Found: C 75.97, H 5.00

20 MS: m/e 268

NMR: 4.82(s, 1H, exchanges with D₂O), 2.24(s, 2H), 7.04-7.40(m, 7H), 7.50-7.71(m, 3H).

25 **(B) N,N-Dimethyl-[6-(2-Fluorobenzyloxy)-2-naphthlyoxy]-thionocarbamate**

A stirred solution of 2.6 g(10 mM) of the intermediate prepared in part (A) in 20 mL of DMF was cooled in a water bath to ca. 25 °C under nitrogen and
30 treated with 0.54 g (13.5 mM) of NaH. After gas evolution had subsided, the mixture was treated with 2.03 g (16.5 mM) of N,N-dimethyl thiocarbamyl chloride. After 3h at ambient temperature, the mixture was treated

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cautiously with 250 mL of 2N HCl to produce a solid which was filtered off and washed with H₂O and Hexane.

Recrystallization of the solid from I-PrOH provided 2.11 g (59%) of product as tan crystals mp 165-165 °C.

5

Anal. Cal. For C₂₀H₁₈FNO₂S (MW 355): C 67.59, H 5.11, N 3.94, S 9.02.

Found: C 67.51, H 4.99, N 3.90, S 8.77

MS: m/e 355

10 NMR: 3.40(bs, 3H), 3.50(bs, 3H), 5.26(s, 2H), 7.00-7.90 (m, 10H).

(C) **N,N-Dimethyl-[6-(2-Fluorobezyl oxy)-2-naphthylthiooxy]-carbamate**

15

A mixture of 2.3 g (6.4 mM) of the intermediate prepared in part (B) above and ca. 5 g of 2-methoxynaphthalene was heated under an air condenser under nitrogen. The resulting molten mass was heated to boiling (ca. 275 °C) for 2h, when TLC demonstrated consumption of the starting material. The cooled mass was chromatographed over Silica with CHCl₃ and the product fractions combined and evaporated. Recrystallization of the dark residue from Me₂CO/hexane with decolorizing carbon afforded 1.0g (48%) of product as white crystals mp 108-109 °C.

20

25

Anal. Cal. For For C₂₀H₁₈FNO₂S (MW 355): C 67.59, H 5.11, N 3.94

30 Found: C 67.73, H 5.15, N 3.68.

MS: m/e 355

NMR: 3.10 (bs, 6H), 5.26(s, 2H), 7.00-7.90 (m, 10H).

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(D) Methyl [6-(2-Fluorobezylloxy)-2-naphthyl]thioacetate.

5 A stirred mixture of 0.9 g (2.5 mM) of the intermediate prepared in (C) and 30 mL of MeOH under nitrogen was treated with 4ml of 2N NaOH (8 mM) and heated to reflux for 6h. The resulting clear solution was cooled in an ice bath, treated with excess 5N HCL and
10 the resulting mixture stirred 8-16 hours. The solid was collected by filtration, washed with H₂O, drained and taken up in 50mL of Me₂CO/5 mL MeOH. The mixture was treated with 2.59 g (18.7 mM) of K₂CO₃, 0.1 g of powdered KI, 1.2 mL (12.6 mM) of methyl bromoacetate and heated to
15 reflux for 3h. The cooled mixture was treated with H₂O and extracted with EtOAc. The EtOAc extracts were washed with H₂O and brine, dried with MgSO₄ and evaporated. The soft slightly yellow solid residue was boiled with hexane to provide 0.6 g (66%) of the product as a soft white
20 powder mp 88-90 °C.

Anal. Cal. For C₂₀H₁₇FO₃S (MW 356): C 67.40, H 4.81.

Found: C 67.27, H 4.99

MS: m/e 356

25 NMR: 3.66 (s, 2H), 3.67 (s, 3H), 5.26 (s, 2H), 7.00-7.90 (m, 10H).

30 (E) Methyl [6-(2-Fluorobezylloxy)-2-naphthylsulfonyl]acetate.

A stirred mixture of 0.5 g (1.4 mM) of the intermediate prepared in (D) above in 10mL of HOAc was

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treated with 5 mL (excess) of 30% H₂O₂ and kept at ambient temperature 24h. the resulting clear solution was diluted with H₂O and extracted with EtOAc. The extracts were washed successively with H₂O, bicarbonate, H₂O, brine, dried with MgSO₄ and evaporated. The white residue was recrystallized from MeOH to provide 0.34 g (62%) of the product as slender needles mp 112-113 °C.

Anal. Cal. For C₂₀H₁₇FO₅S (MW 388): C 61.85, H 4.41, S 8.25.
Found: C 61.60, H 4.33, S 8.17.
MS: m/e 388
NMR: 3.70(s, 3H), 4.20(s, 2H), 5.30(s, 2H), 7.00-7.90 (m, 10H).

15

(F) (E/Z) Methyl 1- [6-(2-Fluorobezoyloxy)-2-naphthylsulfonyl]-2-N,N-dimethylamino acrylate

A solution of 0.81 g (2 mM) of the intermediate prepared as in part (E) above in 20 mL of THF was treated with 1.6 mL (9 mM) of DMA. The resulting brown solution was kept at ambient temperature under nitrogen for a total of 48h, with an intermediate period of heating for 4h. Evaporation of the solution provided a thick brown liquid which solidified on trituration with Et₂O. Recrystallization of the residue from MeOH provided 0.72 g (78%) of product as a tan powder mp 128-129 °C.

Anal. Cal. For C₃₂H₂₂FNO₅S (MW 443): C 62.29, H 5.00, N 3.16, S 7.23.
Found: C 62.31, H 5.02, N 3.09, S 7.38.
MS m/e 444

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NMR: 2.99(bs, 3H), 3.35 (bs, 3H), 3.50 (s, 3H), 5.30 (s, 2H), 7.00-7.90 (m, 10H).

5 (G) 6-(2-Fluoro benzyloxy)-2-naphthylsulfonyl-
pyrazolin-3-one

A stirred mixture of 0.72 g (1.6 mM) of the intermediate prepared as in part(F) and 20 mL of EtOH was treated with 1.0 mL of 85% hydrazine hydrate and heated
10 to reflux for 2h. The resulting solution was cooled, diluted with H₂O and filtered to remove a solid. The aqueous alcohol filtrate was acidified to pH 2 and extracted with EtOAc. The extracts were washed with H₂O, brine, dried with MgSO₄ and evaporated. The residual
15 solid was washed with small portions of cold MeOH to provide 0.15g (23%) of the product as a white powder mp 283-285 °C (dec.)

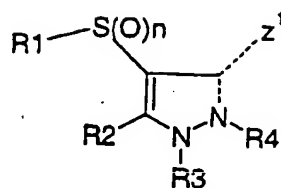
Anal. Cal. For C₂₀H₁₅FN₂O₄S (MW 398): C 60.30, H 3.80, N
20 7.03, S 8.05.

Found: C 60.30, H 4.08, N 6.92, S 7.75

MS: m/e 397.

Claims:

- 5 1. A compound of formula I:



I

10

wherein:

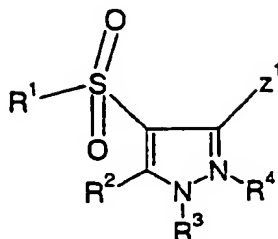
R¹, R², R³, and R⁴ are independently alkyl, aryl, aralkyl, heteroaryl, heteroalkyl radicals of 1-20 atoms (including, but not limited to, carbon, hydrogen, oxygen, nitrogen, sulfur, phosphorus, halogen) with or without
15 alkyl, aryl, aralkyl or heterocyclic radical substituents;

Z¹ is hydrogen, oxygen, sulfur, or nitrogen; and is attached by a single or double bond, provided that when
20 the dashed bond in the ring is a double bond, Z¹ is attached via a single bond;

n is an integer from zero to 2; and

pharmaceutically acceptable salt or prodrug thereof.

2. A compound of formula III:

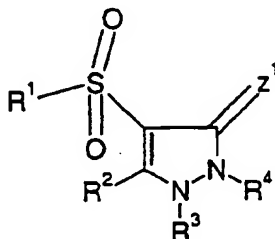


III

wherein:

R¹, R², Z¹ are as described above and R³, R⁴ are Hydrogen.

3. A compound of formula IV:



IV

wherein;

R², R³ and R⁴ are hydrogen; and

Z¹ is oxygen, NR⁵ or S, and wherein R⁵ is selected from the group consisting of H, C₁-C₄ alkyl, phenyl or benzyl.

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4. The compound according to Claim 1 wherein R¹ and R² are hydrogen and R³ is a group selected from the group consisting of alkyl, aryl, aralkyl, and alkylaryl..

5 5. A compound according to Claim 1 selected from the group consisting of:

4 - (4-[2-(2-Phenyl-4-oxazolyl)ethoxy]phenylsulfonyl)-1H,2H-pyrazolin-3-one; 4 - (4-[2-(2-Phenyl-4-oxazolyl)ethoxy]phenylmethylsulfonyl)-1H,2H-pyrazolin-3-one; 3-(4-(2-Phenyl-4-oxazolyl)ethoxy)phenyl-4-methylsulfonyl-1H-1,2-pyrazoline; 2-Naphthylsulfonyl-pyrazolin-3-one; and 6-(2-Fluorobenzyloxy)-2-naphthylsulfonyl-pyrazolin-3-one; or a pharmaceutically acceptable salt or prodrug thereof.

15

6. A pharmaceutical formulation comprising a compound of formula (I), together with one or more pharmaceutically acceptable carriers, diluents, or excipients.

20

7. A method of treating hyperglycemia in a mammal including a human in need thereof, comprising administering to said mammal an effective amount of a compound of Claim 1.

25

8. A method of treating hyperlipidemia in a mammal including a human in need thereof, comprising administering to said mammal an effective amount of a compound of Claim 1.

30

9. A method of treating hyperglycemia comprising administering to a mammal including a human in need thereof, an effective amount of a compound of Claim 3.

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10. A method of treating hyperlipidemia comprising administering to a mammal including a human in need thereof, an effective amount of a compound of Claim 3.

5

11. A pharmaceutical composition comprising a compound of formula (I) for the treatment of a mammal including a human afflicted with hyperlipidemia.

10

12. A pharmaceutical composition according to formula (I) for the treatment of a mammal including a human afflicted with hyperglycemia.

15

13. A compound of the formula (I) or a pharmaceutically acceptable salt thereof, as claimed in any one of Claims 1 or 2 or 3 for use in treating hyperglycemia.

20

14. A compound as claimed in any one of Claims 1 or 2 or 3 for use in treating hyperlipidemia.

25

15. Use of a compound of formula (I) in the manufacture of a medicament for the treatment of hyperglycemia.

16. Use of a compound of formula (I) in the manufacture of a medicament for the treatment of hyperlipidemia.

30

17. Use of a compound selected from the group consisting of:

4 - (4-[2-(2-Phenyl-4-oxazolyl)ethoxy]phenylsulfonyl)-1H,2H-prazolin-3-one;

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4 -(4-[2-(2-Phenyl-4-oxazolyl)ethoxy]phenylmethylsulfonyl)-1H,2H-prazolin-3-one;
3-(4-(2-Phenyl-4-oxazolyl)ethoxy)phenyl-4-methylsulfonyl-
5 1H-1,2-pyrazoline;
2-Naphthylsulfonyl-pyrazolin-3-one; and
6-(2-Fluorobenzyloxy)-2-naphthylsulfonyl-pyrazolin-3-one;
or a pharmaceutically acceptable salt or prodrug thereof
for the manufacture of a medicament for the treatment of
10 hyperglycemia.

18. Use of a compound selected from the group consisting of:

4 -(4-[2-(2-Phenyl-4-oxazolyl)ethoxy]phenylsulfonyl)-1H,2H-prazolin-3-one;
15 4 -(4-[2-(2-Phenyl-4-oxazolyl)ethoxy]phenylmethylsulfonyl)-1H,2H-prazolin-3-one;
3-(4-(2-Phenyl-4-oxazolyl)ethoxy)phenyl-4-methylsulfonyl-
20 1H-1,2-pyrazoline;
2-Naphthylsulfonyl-pyrazolin-3-one; and
6-(2-Fluorobenzyloxy)-2-naphthylsulfonyl-pyrazolin-3-one;
or a pharmaceutically acceptable salt or prodrug thereof
for the manufacture of a medicament for the treatment of
25 hyperlipidemia.

19. An article of manufacture comprising packaging material and a compound of formula I contained within said packaging material wherein the compound of formula I
30 is therapeutically effective for the treatment of hyperglycemia and/or hyperlipidemia and wherein the packaging material comprises a label which indicates that the pharmaceutical agent can be used for the treatment of hyperglycemia and/or hyperlipidemia.

20. A compound as disclosed in anyone of the examples herein described.

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